Total Synthesis of (-)-Mersicarpine

Rie Nakajima, Tsuyoshi Ogino, Satoshi Yokoshima, and Tohru Fukuyama. *J. Am. Chem. Soc*. ASAP

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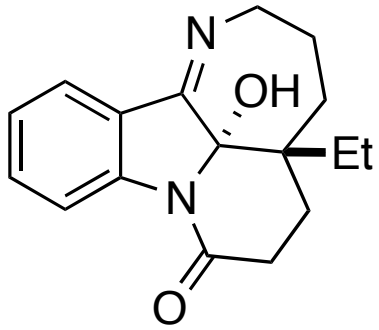


Eric E. Buck
Current Literature
January 23, 2010

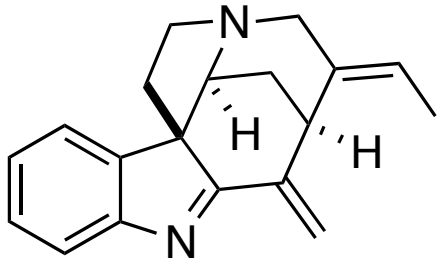
Isolation and Background

• (-)-Mersicarpine was isolated from the bark of *K. fruiticosa* and *K. arborea in 2004.*

• *Kopsia* genus comprises over 23 shrubs and trees in tropical Asia with the highest concentration found in Malaysia

• Over 50 different alkaloids have been isolated from *K. arborea*.

• A select few of the isolated alkaloids, most notably, valparicine, have demonstrated cytotoxic properties against drug-resistant KB cells (IC_{50} 2.72 μM).

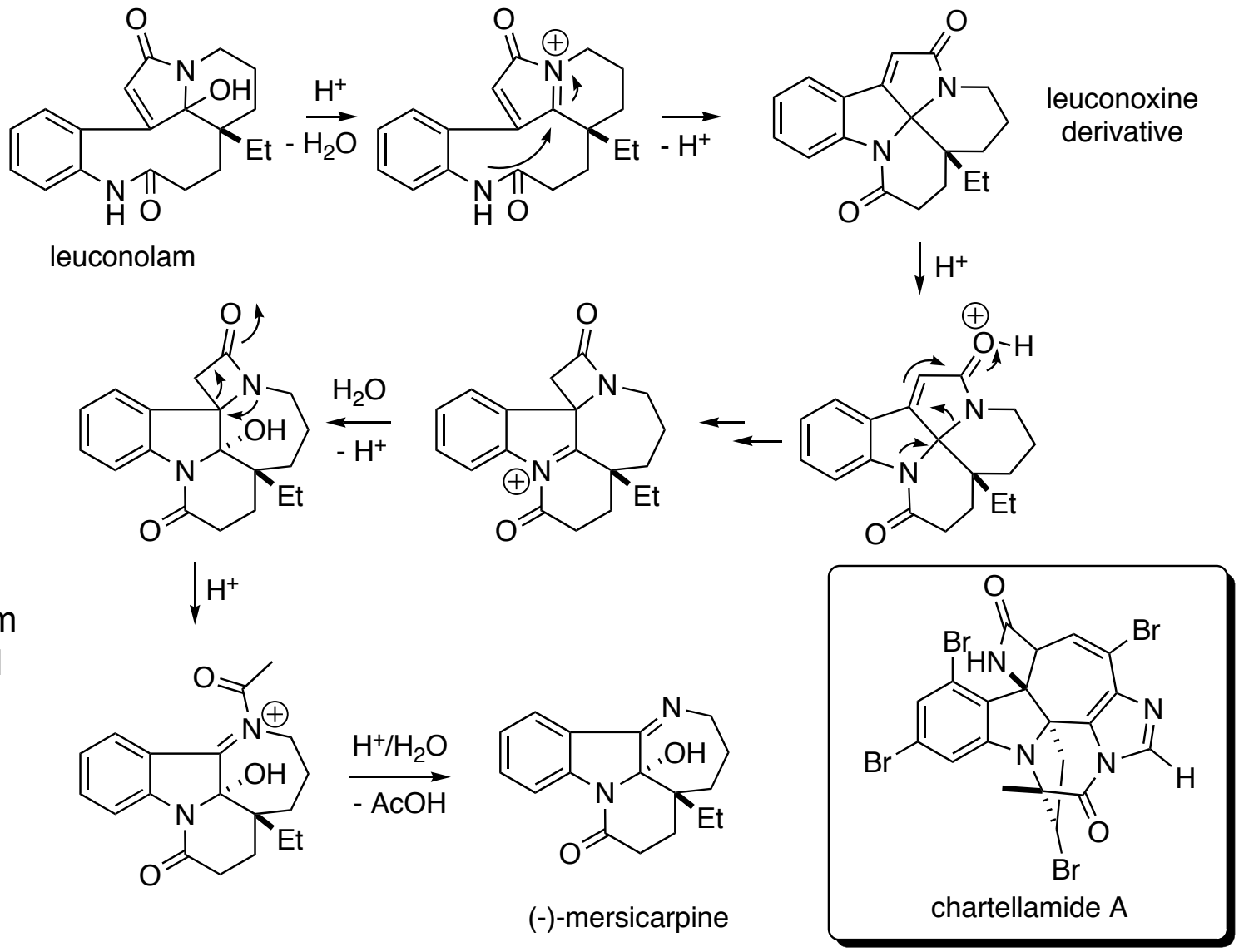


valparicine

Lim, K.; Hiraku, O.; Kanki, K.; Koyano, T.; Hayashi, M.; Kam, T. *J. Nat. Prod.* **2007**, 70, 1302-1307

Kam, T.; Subramaniam, G.; Lim, K.; Choo, Y. *Tetrahedron Lett.* **2004**, 45, 5995-5998

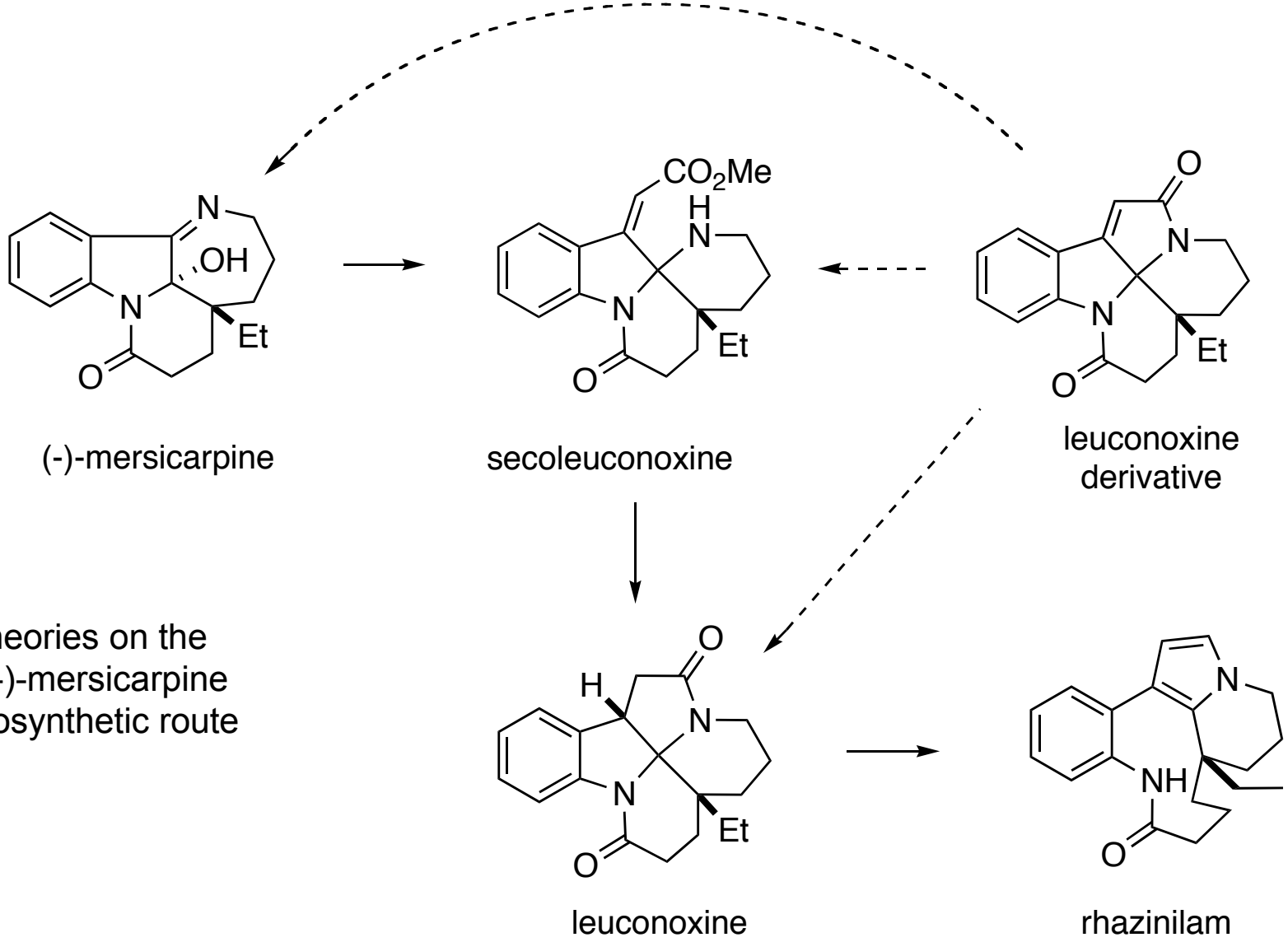
Proposed Biosynthesis



• Water adds from the less hindered face.

Kam, T.; Subramaniam, G.; Lim, K.; Choo, Y. *Tetrahedron Lett.* **2004**, 45, 5995-5998

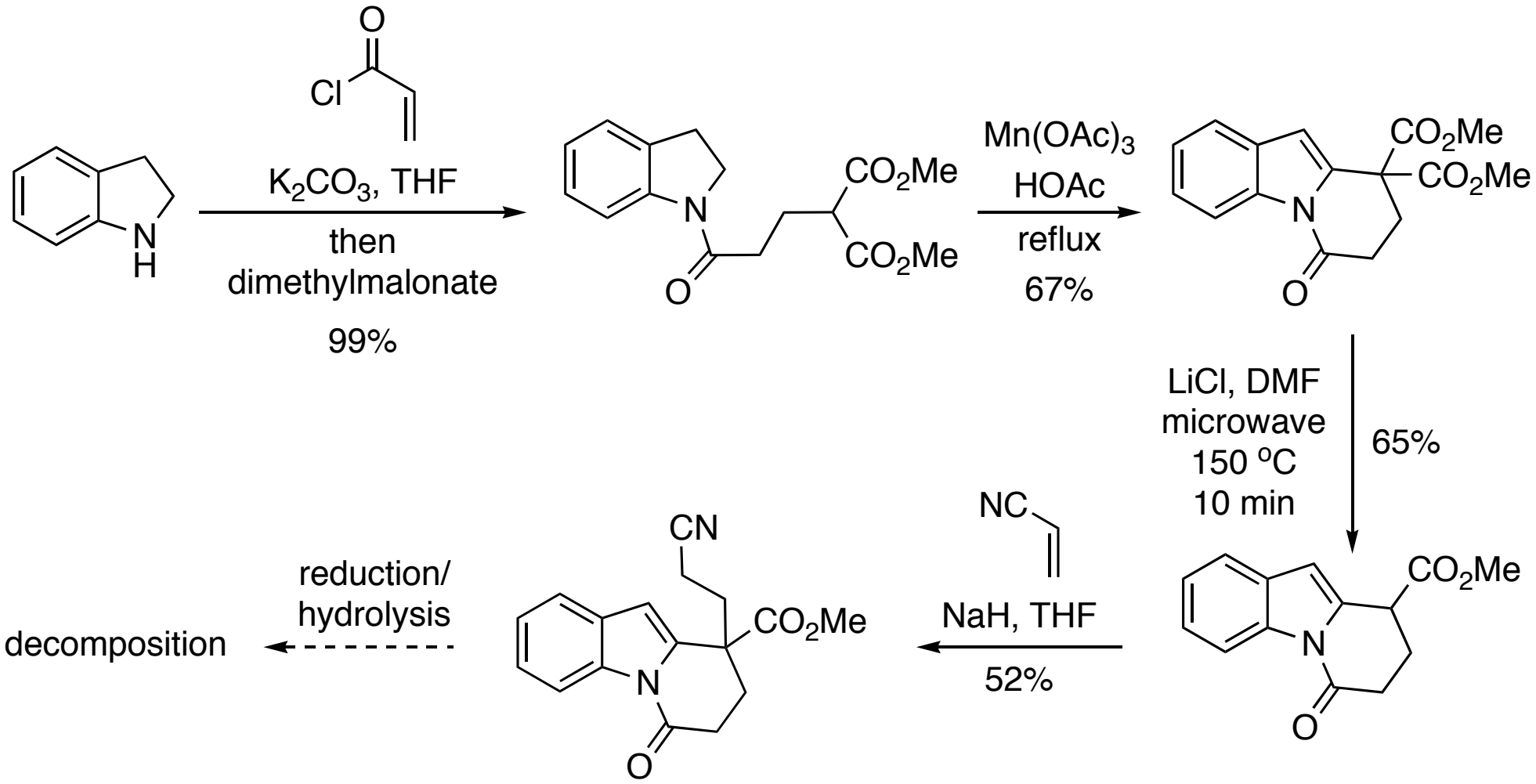
Postulated biosynthesis of other isolated alkaloids by the Kerr group



• Different theories on the location of (-)-mersicarpine along the biosynthetic route

Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, 10, 1437-1440

The Kerr group's synthesis of (±)-mersicarpine



- Very labile indole-amide functionality.

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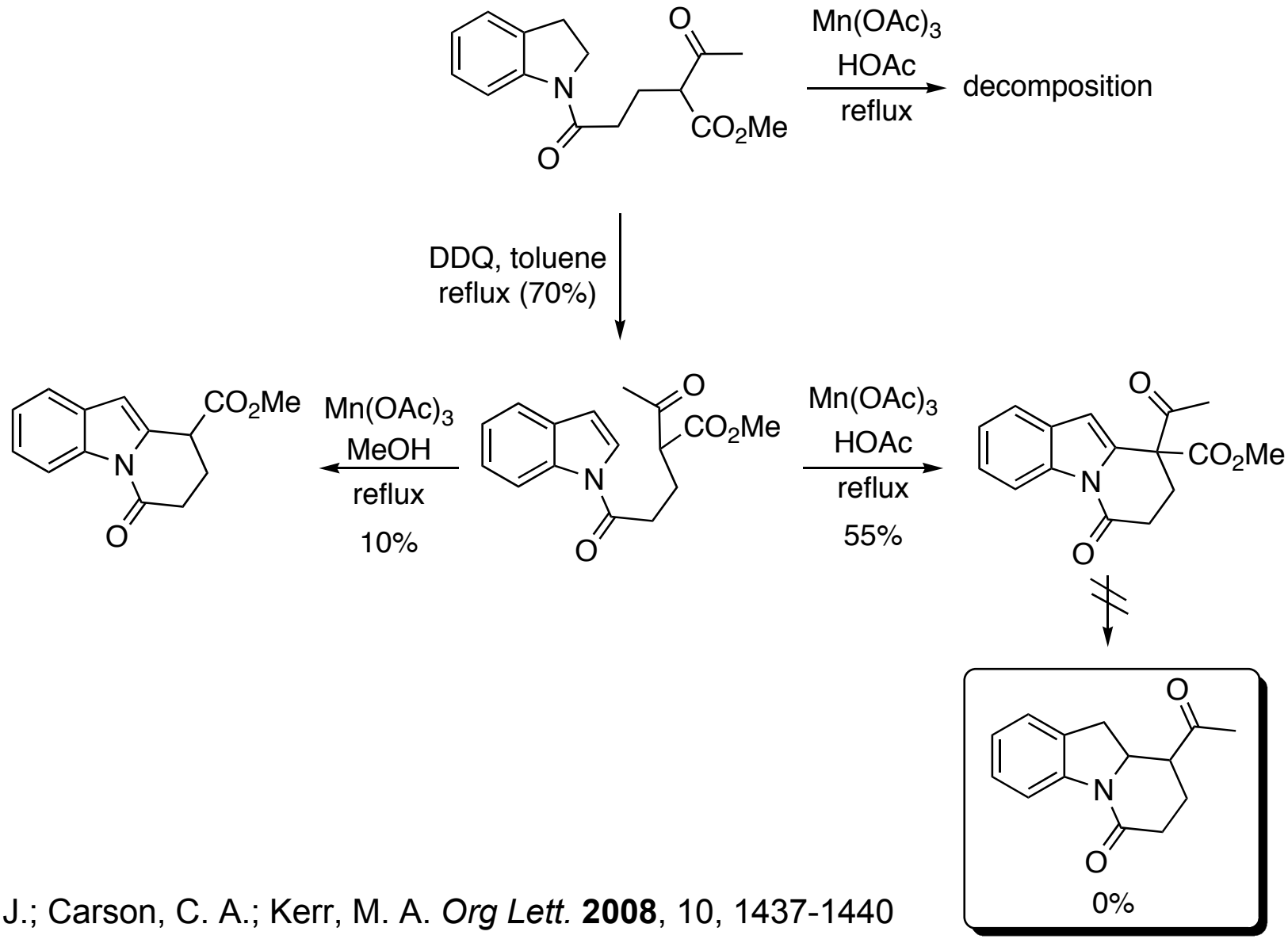

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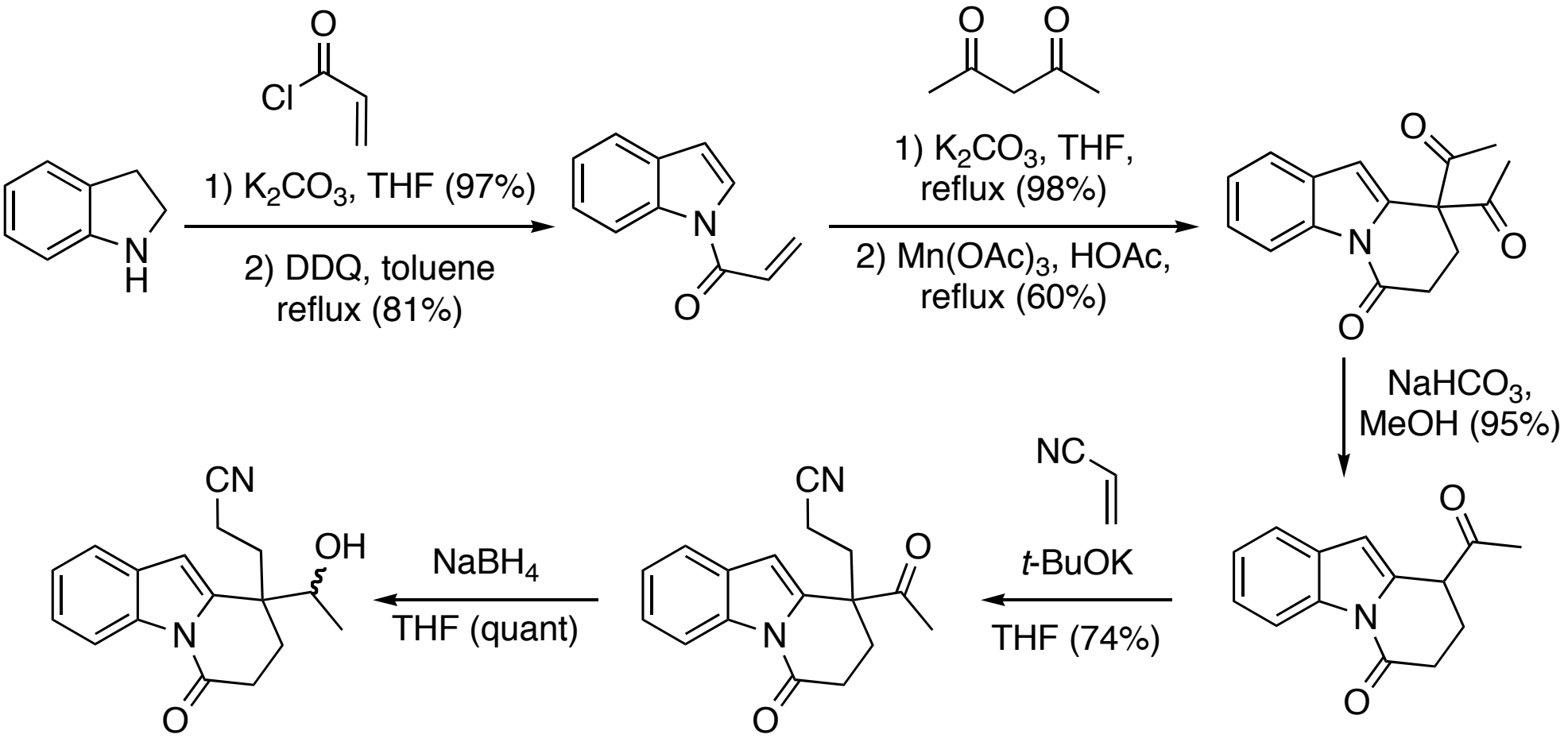

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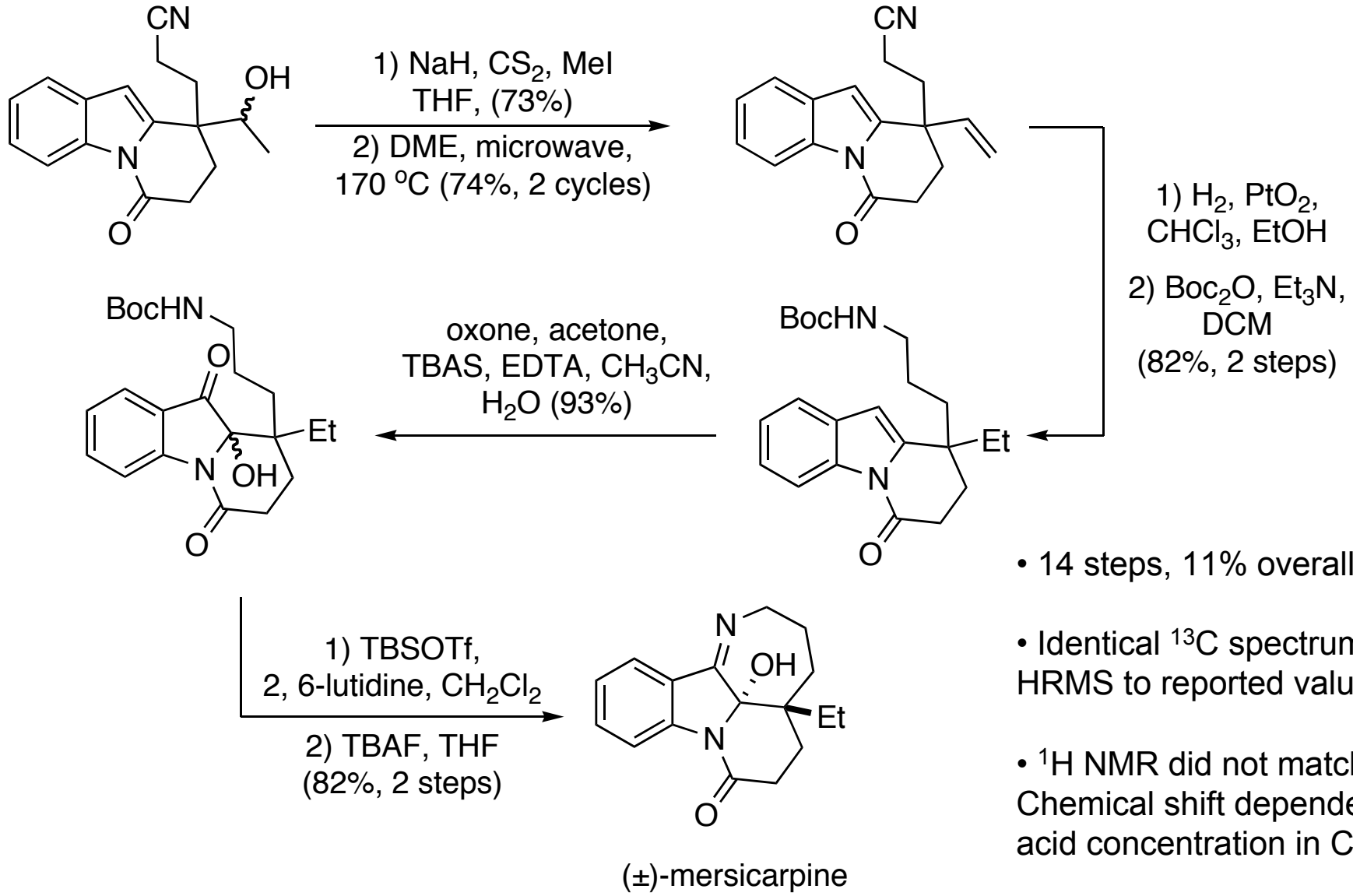
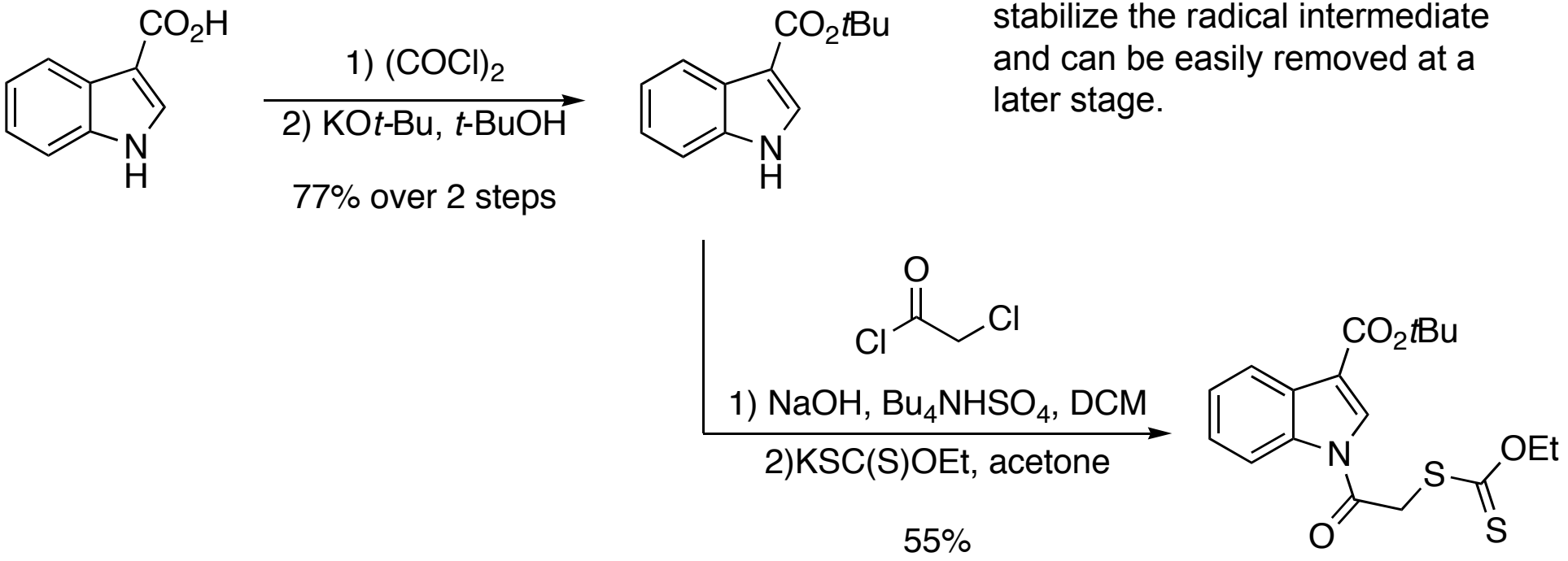


(±)-mersicarpine

- 14 steps, 11% overall yield
- Identical ^{13}C spectrum and HRMS to reported values
- ^{1}H NMR did not match. Chemical shift dependent on acid concentration in $CDCl_3$

Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, 10, 1437-1440

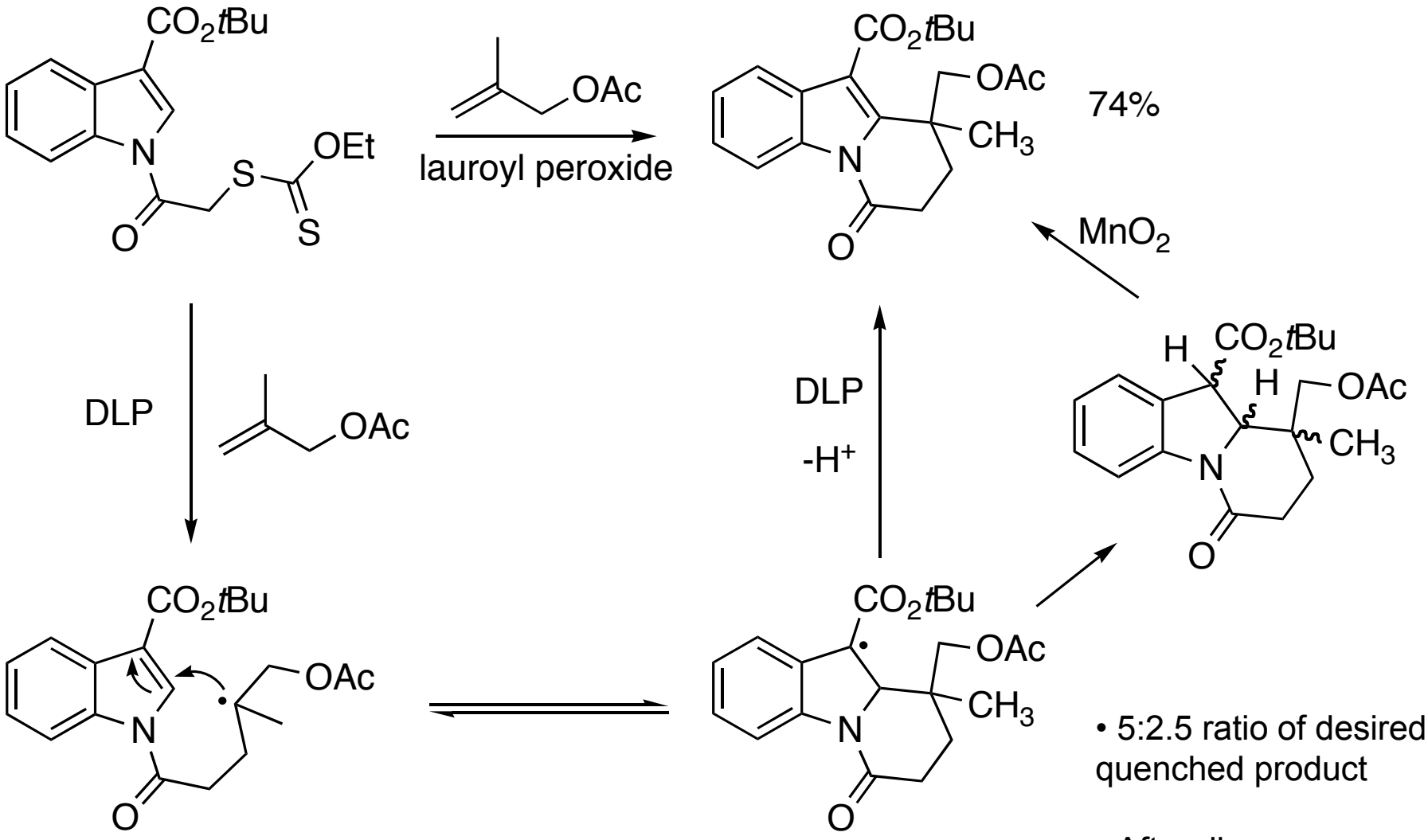
The Zard group's formal synthesis of (±)-mersicarpine



• The *t*-butyl ester serves to stabilize the radical intermediate and can be easily removed at a later stage.

Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

The Zard group's formal synthesis of (±)-mersicarpine

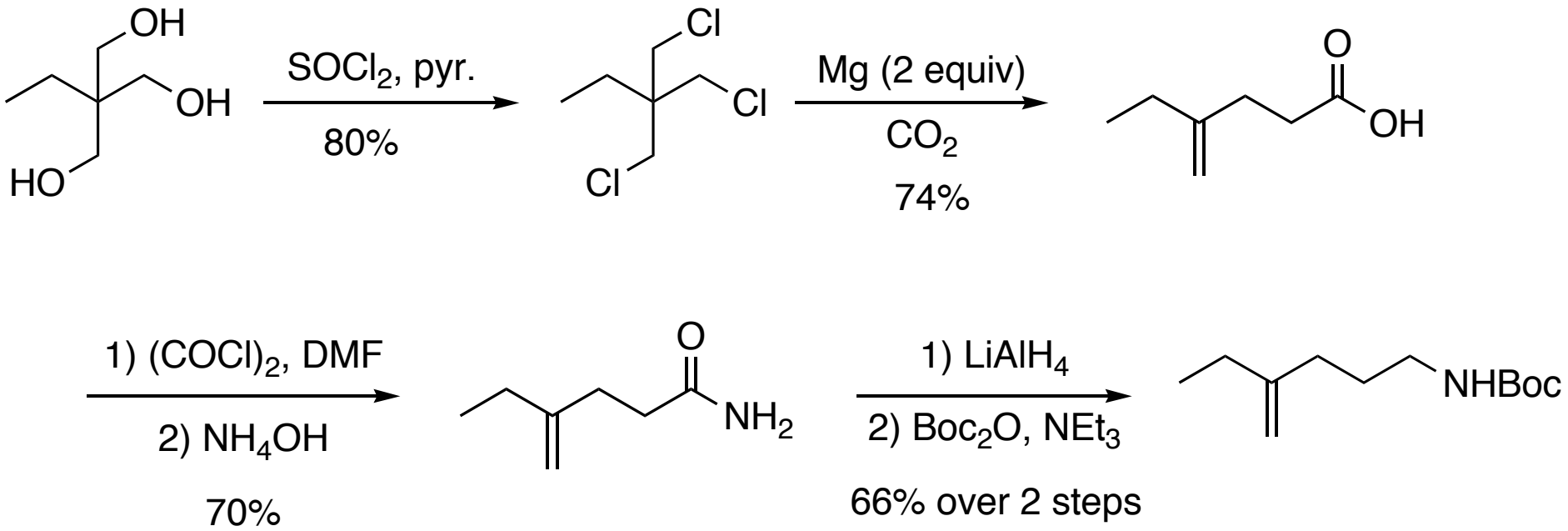


• 5:2.5 ratio of desired: quenched product

• After disappearance of SM MnO_2 was added.

Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

The Zard group's formal synthesis of (±)-mersicarpine



For preperation of 4-ethyl-4-pentenoic acid see: McCaffery, E. L.; Shalaby, S. w. *J. Organomet. Chem.* **1967**, 8, 17-27
For preperation of 4-ethyl-4-pentenamide see: Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803
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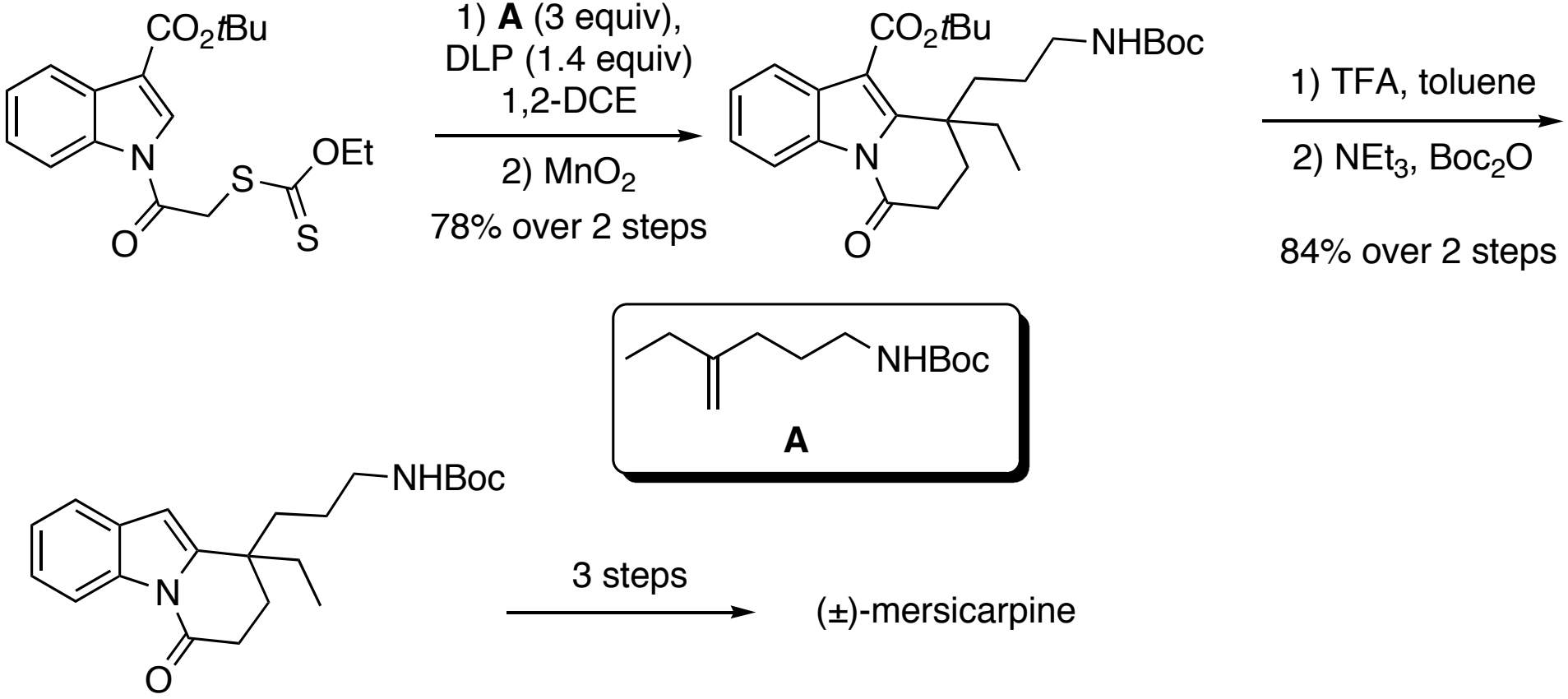
The Zard group's formal synthesis of (±)-mersicarpine

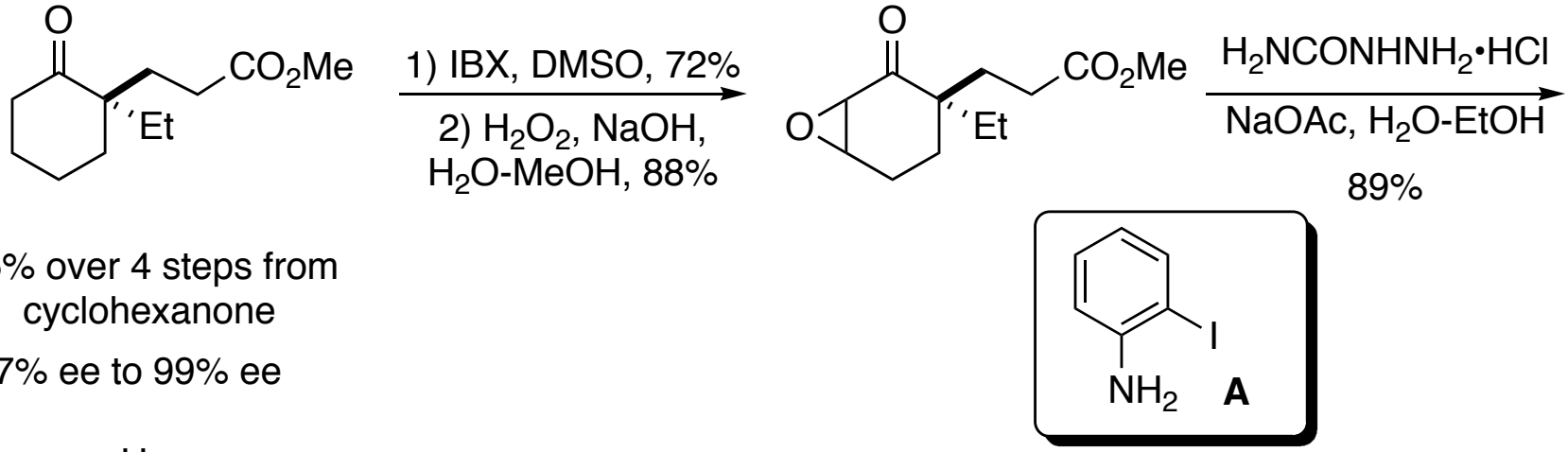


Kerr's advaced intermediate

- 10 steps to Kerr's advanced intermediate in 18% yield (1 fewer step).

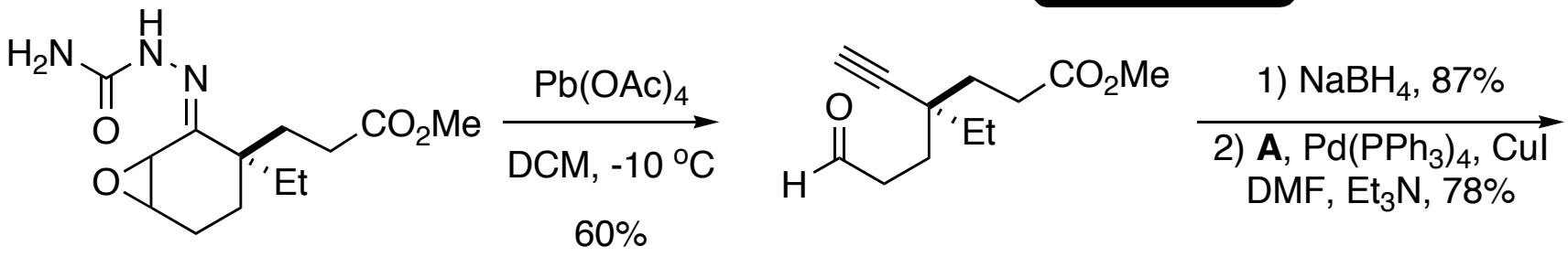
Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

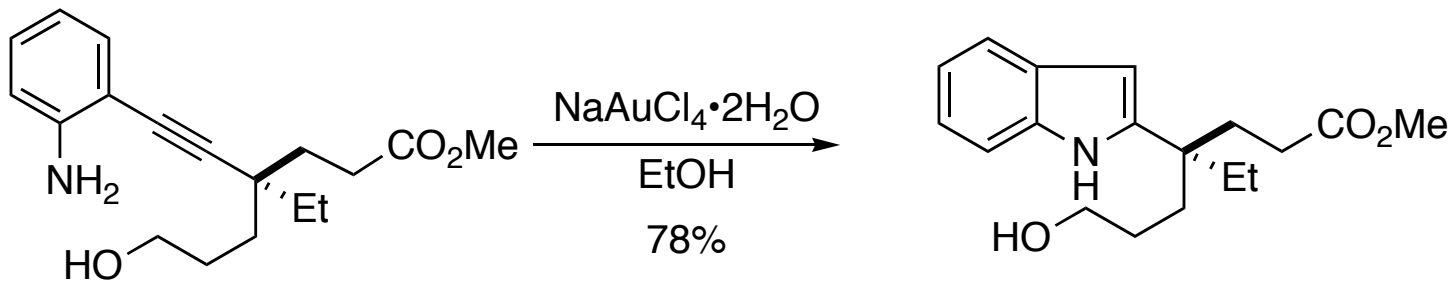
Title Paper: Eschenmoser-Tanabe fragmentation and indole formatior



25% over 4 steps from cyclohexanone

87% ee to 99% ee





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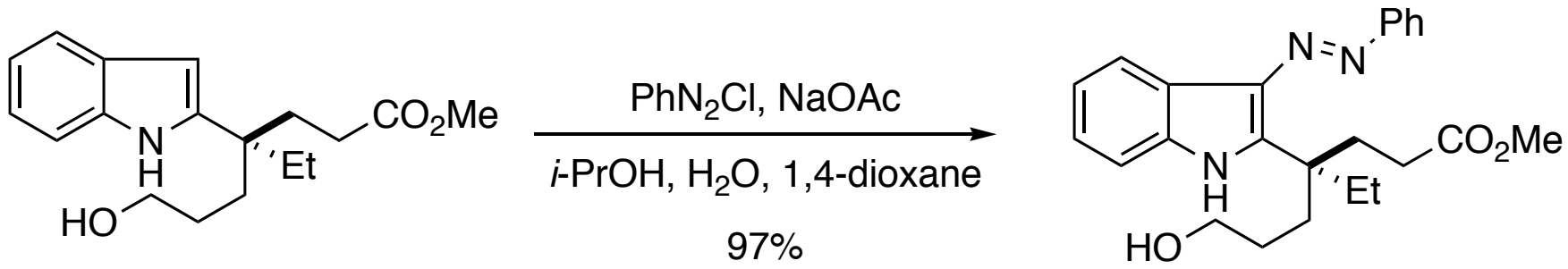
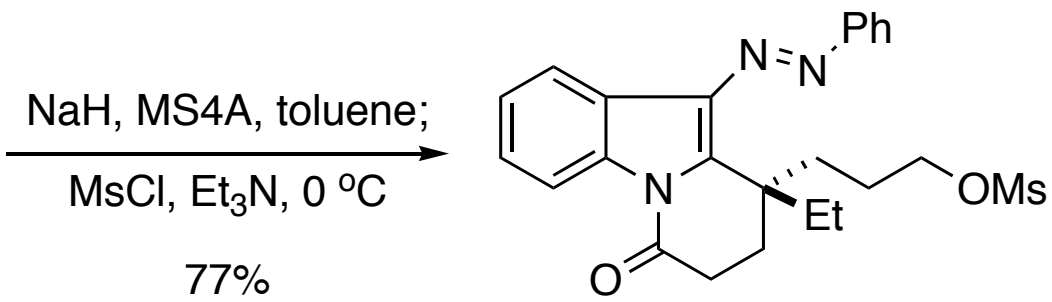
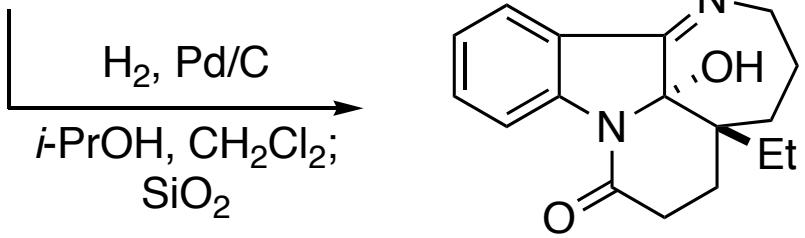
Title Paper: Unexpected oxidation





- Unexpected formation of (-)-mersicarpine after prep-TLC purification. Yield were low and irreversible however.



(-)-mersicarpine

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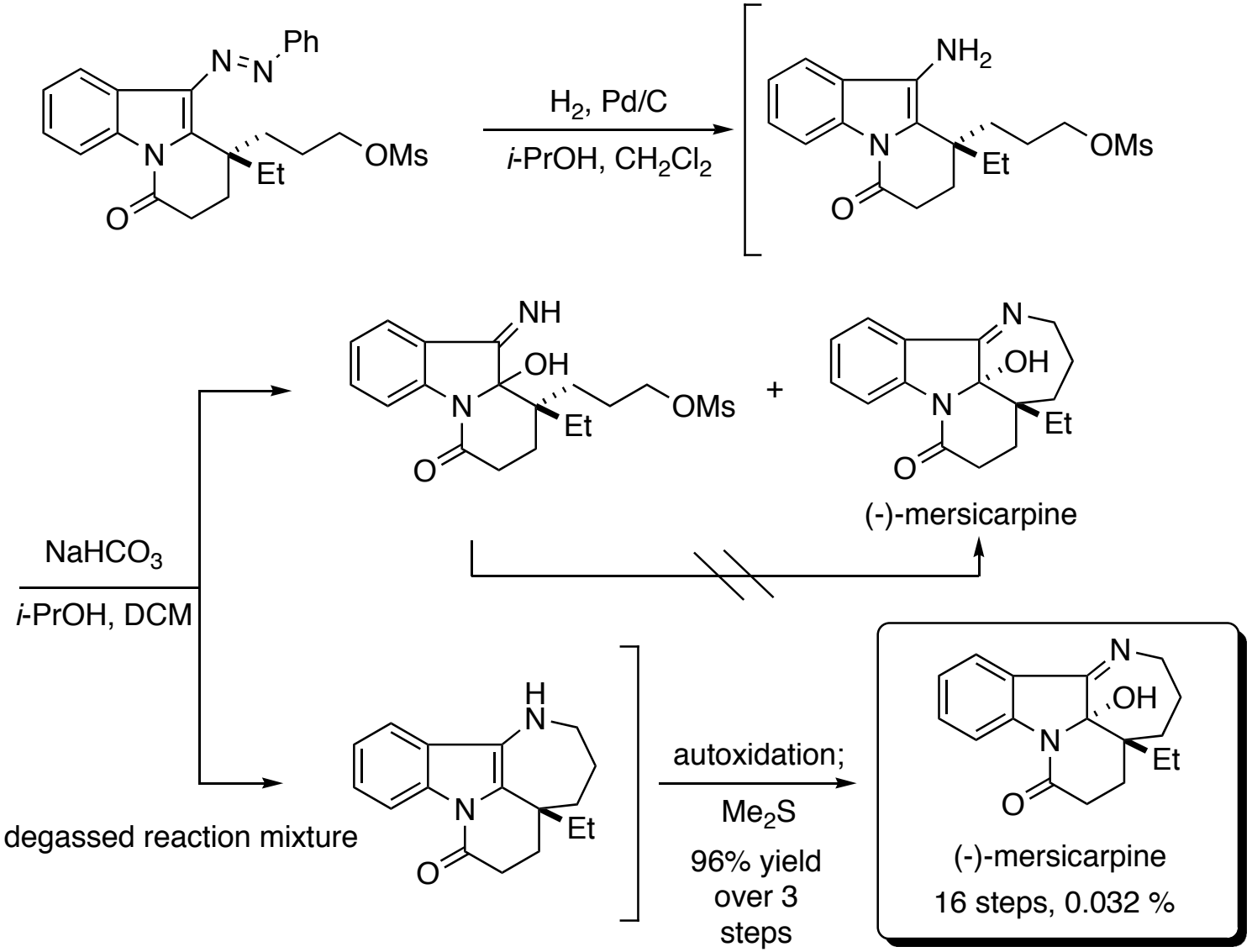
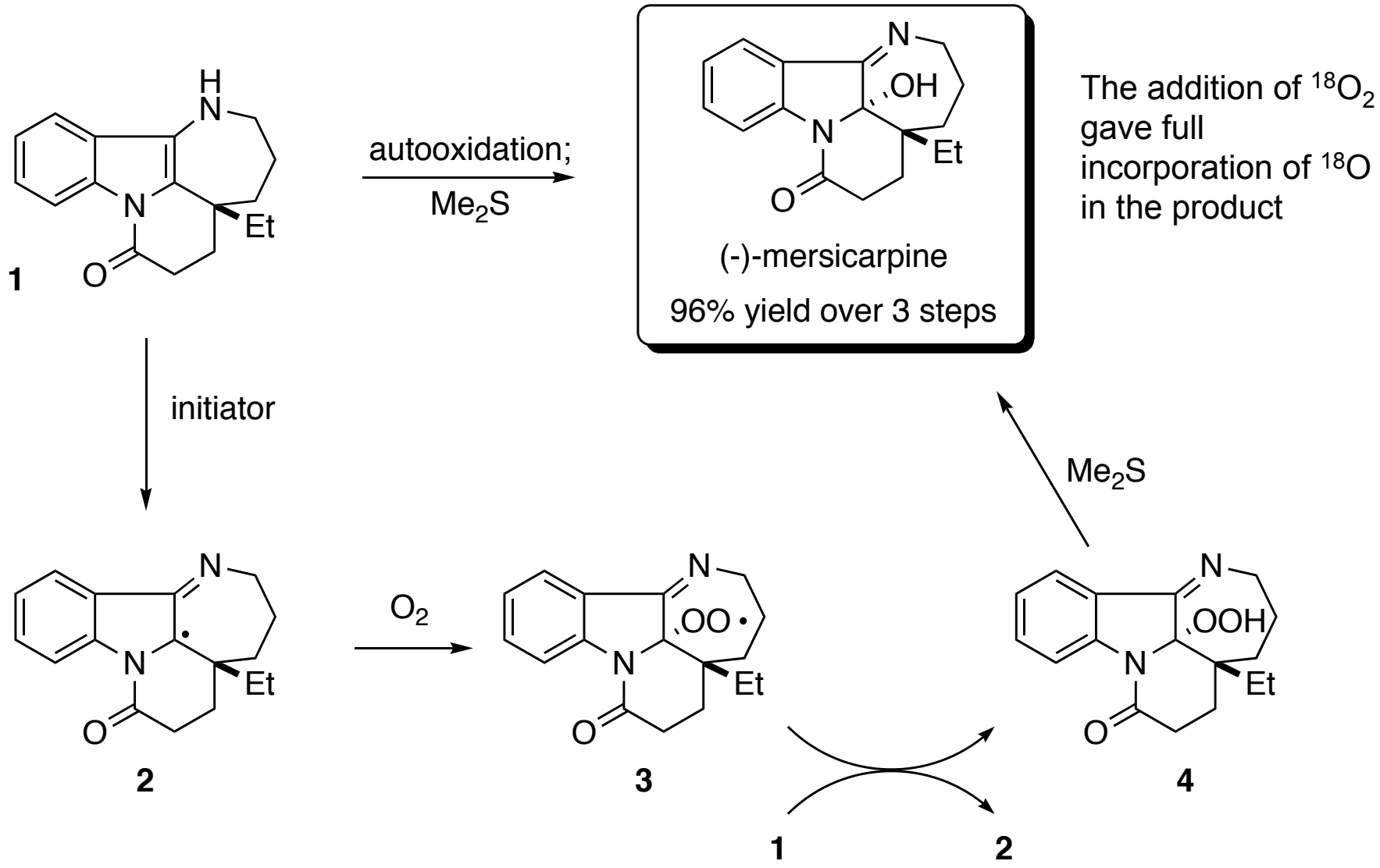
Title Paper: Control of autoxidation



Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* ASAP

Title Paper: Proposed mechanism of final oxidation



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Summary

• 2 distinct approaches to assemble the core

• The Kerr group constructed (±)-mersicarpine in 14 steps and 11% yield utilizing an oxidation/ radical cyclization sequence to construct the 6 membered ring followed by an imine cyclization to install the 7-memebered ring.

• The Zard group constructed an advanced intermediated of the Kerr group's (±)-mersicarpine synthesis in 10 steps and 18% yield utilizing an a radical annulation sequence to construct the 6 membered ring.

• The Fukuyama group completed the total synthesis of (-)-mersicarpine in 10 steps and 3.2 % yield from known cyclohexane. They utilized a Sonogashira coupling and gold catalyzed annulation to install the indole moiety followed by acylation sets the 6 membered ring.